3-8-91

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(EXCERPT)

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March 8, 1991

DATA EVALUATION RECORD

SULFOSATE

Metabolism in Rats

STUDY IDENTIFICATION: Boberg, E. W., and Ritter, J. C. ICIA-0224: Metabolism study in rats. (Unpublished Study No. T-12906 performed by ICI Americas, Inc., Farmington, CT; dated December 20, 1988.) MRID No. 412359-03.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 3/6/91

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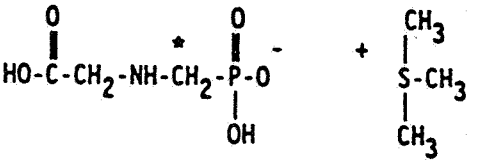
1. CHEMICAL: Sulfosate; ICIA-0224; trimethylsulfonium carboxymethylaminomethylphosphonate.

2. TEST MATERIAL: Unlabeled sulfosate (technical grade) and sulfosate labeled with ^{14}C at the methyl-phosphonate site were used. The unlabeled test material (lot No. WRC-8865-20-01) contained 56.2% active ingredient and 41% water. The specific activity and radiochemical purity of ^{14}C-labeled sulfosate (lot No. WRC-8917-23-01) were 9.8 mCi/mmol and 93.2%, respectively. The structure and radiolabel position (*) of [^{14}C]sulfosate are shown below:



3. STUDY/ACTION TYPE: Metabolism in rats.

4. STUDY IDENTIFICATION: Boberg, E. W., and Ritter, J. C. ICIA-0224: Metabolism study in rats. (Unpublished Study No. T-12906 performed by ICI Americas, Inc., Farmington, CT; dated December 20, 1988.) MRID No. 412359-03.

5. REVIEWED BY:

Mary E. Cerny, M.S.
Principal Reviewer
Dynamac Corporation

Signature: Mary E. Cerny
Date: 3/7/91

William L. McLellan, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: William L. McLellan
Date: 3/7/91

6. APPROVED BY:

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation

Signature: William L. McLellan for
Date: 3-7-91

Nguyen B. Thoa, Ph.D.
EPA Reviewer, Section I
Toxicology Branch I
(H-7509C)

Signature:
Date: 3/11/91

Roger Gardner, Ph.D.
EPA Section Head, Section I
Toxicology Branch I
(H-7509C)

Signature: Roger Gardner
Date: 3-12-91

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7. CONCLUSIONS:

A. [^{14}C]Sulfosate administered to rats was readily absorbed and rapidly eliminated. Approximately 90% of a single intravenous (iv) dose was excreted in the urine. Following administration of a single oral dose (25 or 250 mg/kg) or repeated oral doses (25 mg/kg), between 70 and 82% of the total radioactivity administered was eliminated within 24 hours and 85 to 94% within 120 hours. After administration of 25 mg/kg (single dose or repeated doses), 47 to 57% of the total radioactivity was excreted in the urine, and 36 to 42% was eliminated in the feces. The patterns of excretion were similar in both sexes. After administration of a single oral dose of 250 mg/kg, absorption was more saturated in females (54% of the radioactivity was eliminated in the feces; 36% was excreted in the urine) than in males (56 and 36% in the urine and feces, respectively). Biliary excretion was low, because only about 4% of an iv dose (25 mg/kg) was found in the feces.

Tissue ^{14}C residue levels were low 5 days after dosing; all tissues combined (including liver, kidneys, brain, heart, spleen, skin, stomach and intestines plus contents, gonads, and blood) contained no more than 0.32% of the radioactive dose, and most ^{14}C tissue concentrations (including those of high-dose rats) were ≤3 ppm. In contrast, carcasses contained up to 2.25% of the ^{14}C dose, with most of the radioactivity found in the bone (2.7 to 7 ppm for low- and repeated-dose rats and 19.4 to 31.8 ppm for high-dose animals). These data suggest that [^{14}C]sulfosate may accumulate in the bones even after a single oral exposure. Repeated dosing did not affect the distribution of [^{14}C]sulfosate; ^{14}C tissue levels in high-dose rats were proportionately higher than those in rats given a 25-mg/kg dose.

Most of the excreted radioactivity (77 to 96% of that in the feces, 80 to 90% of that in the urine) was recovered as unchanged anion (carboxymethylaminomethyl phosphonate). Several minor metabolites, each generally accounting for less than 3% of the excreted radioactivity, were also isolated. One compound recovered from the feces of repeated-dose females was tentatively identified as the decarboxylated metabolite aminomethylphosphonic acid. Other metabolites were not identified or characterized. Repeated oral exposure to sulfosate seemed to cause a slight increase in the production of some unidentified urinary metabolites.

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B. This study is acceptable and was conducted essentially according to EPA Guideline 85-1.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS:

A. Materials and Methods:

1. The radiopurity of [^{14}C]sulfosate (lot No. NRC-8917-23-0) was determined, according to the protocol supplied by the study authors (CBI p. 49), by either thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC) to be 93.2%. (The supplier, Stauffer Chemical Company, Richmond, CA, listed the material's radiopurity as 95.9%.) The detailed methodology used was not described in the materials and methods section of the report. The specific activity of the ^{14}C-labeled sulfosate was 9.8 mCi/mmol. Unlabeled test material (lot No. C-8865-20-01) was 56.2% sulfosate and 41% water; no other components were listed. No additional details were provided.

2. Male and female Sprague-Dawley CRCrl:CD(SD)BR rats were purchased from Charles River Breeding Laboratories (Kingston, NY). The animals were 7 to 9 weeks old at the start of the study and weighed between 159 and 214 g (females) and 208 and 286 g (males). They were quarantined in steel cages for at least 7 days and then were acclimated in individual metabolism cages for 5 days. Animals were fasted for at least 8 hours before dosing.

3. Dosing solutions were prepared by mixing [^{14}C]sulfosate with unlabeled sulfosate and dissolving the mixture in distilled water. The ^{14}C content of each dosing solution was determined by liquid scintillation counting (LSC). Solutions were administered using a dose volume of approximately 2.0 mL/kg; each animal received a total radioactive dose of 50 µCi. The test material was stable in water at 4°C and at room temperature for 4 weeks (CBI p. 52). The unlabeled dosing solutions used in the 14-day repeated-dose study were prepared prior to study initiation and used throughout the dosing period. The doses used in this study were actual doses of the active ingredient.

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[1]Only items appropriate to this DER have been included.

4. Groups of 10 rats (5/sex) were given, by gavage, either a single dose of 25 mg [^{14}C]sulfosate/kg (low-dose group), a single dose of 250 mg [^{14}C]sulfosate/kg (high-dose group), or a single dose of 25 mg unlabeled sulfosate/kg/day for 14 consecutive days followed by a single dose of 25 mg [^{14}C]sulfosate/kg on day 15 (repeated-dose group). An additional group of six rats/sex received a single iv dose (via the tail vein) of 25 mg [^{14}C]sulfosate/kg. Aliquots of the dosing solutions were analyzed by LSC, and the weights of the dosing syringes were taken before and after compound administration to determine the actual dose delivered.

   Urine and feces were collected separately over dry ice 6, 12, 24, 36, 72, 96, and 120 hours after dosing. Expired air was not collected since a pilot study indicated that only negligible amounts of [^{14}C]CO_2 were recovered in the air exhaled by rats given oral doses of [^{14}C]sulfosate (CBI pp. 13, 22). All animals were sacrificed 5 days after administration of the test material, and the following were collected for analysis: liver; kidneys; brain; small and large intestines plus contents; stomach plus contents; gonads; heart; spleen; lungs; samples of mesenteric fat, skeletal muscle, skin, and bone; and carcasses. The metabolic cages were rinsed with distilled water and a detergent and were wiped down to ensure maximal recovery of radioactivity The washes and wipes were collected for radioassaying.

5. Urine and plasma were analyzed directly for ^{14}C content by LSC. Whole blood and red blood cells were solubilized and decolorized prior to analysis. Feces and gastrointestinal contents were homogenized in water, combusted, and analyzed for radioactive content. Tissue samples were homogenized when necessary, solubilized by incubation (in Soluene® 350), and counted. Carcasses were incubated overnight at 60°C in 15% KOH. The KOH-soluble portion was decanted and analyzed by LSC. Bone samples and KOH-insoluble portions of the carcass were incubated in 70% perchloric acid and 30% hydrogen peroxide at 70°C for 2 hours. Following this solubilization step, the samples were analyzed for ^{14}C content. Appropriate measures were taken to determine counting efficiencies and to minimize color quenching.

6. Urinary and fecal sulfosate metabolites were characterized by TLC. Prior to spotting, the silica gel plates were sprayed until saturation with a solution of 0.25 M K_2HPO_4 and 0.25 M K_3PO_4 (pH 12.3), blotted dry, and stored. After spotting, the plates were developed with

methanol:water (1:1, v/v). X-ray film was exposed to the TLC plates for visualization of metabolite spots. Radioactive areas were scraped off and assayed by LSC. Parent compound and one metabolite were characterized further by capillary gas chromatography/mass spectrometry (GC/MS).

Urine collected 0 to 72 hours after dosing was pooled by dose group. An aliquot of each pooled sample was filtered, evaporated to dryness, and redissolved in distilled water. Aliquots of the reconstituted urine were analyzed by TLC (as described above) and LSC. The major urinary metabolite was isolated from urine of high-dose rats and characterized further by TLC. Following chromatographic development, the radioactive band corresponding to this metabolite was scraped off the plate, mixed with acetic anhydride and anhydrous ethanol, and evaporated under nitrogen. The derivatized metabolite was then extracted with ethyl acetate and centrifuged; the supernatant was filtered, concentrated under nitrogen, and analyzed by capillary GC/MS. All feces samples were also pooled by dosing regimen prior to metabolite characterization. Portions of each pooled sample were extracted four times with distilled water; supernatants were combusted, filtered, and then concentrated by evaporation. TLC was performed on the concentrated extracts, and the distribution of ^{14}C on the plates was determined by autoradiography and LSC. The major fecal metabolite was isolated for spectral analysis, as described above.

7. Data were analyzed statistically using Duncan's multiple range test and a p level of 0.05 for detecting significant differences between groups.

B. Protocol: A protocol and protocol deviations for this study are presented in the Appendix.

12. REPORTED RESULTS:

A. Animals in the high-dose group received actual doses of 255 to 334 mg [^{14}C]sulfosate/kg (average ± S.D. = 299 ± 25 mg/kg). Rats in the low-dose groups received actual doses of 22.0 to 33.2 mg/kg (average ± S.D. = 26.4 ± 2.2 mg/kg).

B. Rats given the high dose were lethargic and dehydrated and had tremors, labored breathing, and excessive tearing for up to 72 hours after compound administration. Three high-dose rats (two males and one female) were severely affected and refused food. One male in the low-dose oral group lost hair from its left foreleg. All females and three of the

five males in the iv-dosed group exhibited orbital bleeding immediately after dosing; iv-dosed females also had labored breathing for about 1 minute postdosing. No other signs of toxicity were reported.

C. [^{14}C]Sulfosate was readily absorbed and eliminated by all animals. Within 24 hours after oral dosing, animals excreted 70.0 to 82.1% of the administered dose (31.8 to 51.8% in the urine and 23.9 to 38.2% in the feces). Within 24 hours of intravenous dosing, approximately 85 and 2% of the dose were recovered in the urine and feces, respectively. Twenty-four-hour average recoveries were not affected ($p < 0.05$) by sex or dosing regimen. Within 5 days after oral dosing, 87.5 to 96.9% of the ^{14}C dose was recovered in the urine, feces, tissues, cage washes, and carcass (Table 1). The high-dose females excreted 36.1% of the administered oral dose in the urine and 53.5% in the feces. In contrast, the other groups excreted more radioactivity in the urine (50.8 to 57% of the administered dose) and less in the feces (35.6 to 42%). The differences between high-dose females and high-dose males or low-dose females were statistically significant ($p < 0.05$). Inter-animal variation in excretion of radioactivity was high, particularly among rats given the high dose. [Individual animal data are not presented in this DER; however, mean and standard deviation data for excretion of ^{14}C can be found in Table 1.] For example, high-dose males excreted 36 to 82% and 9 to 56% of the ^{14}C dose in the urine and feces, respectively, within 5 days; corresponding values for females were 20 to 54% and 33 to 71%. An increase in urinary excretion of ^{14}C was associated with an increase in toxicity of the test material. Thus, the three high-dose animals that showed severe toxic signs excreted approximately twice as much of the ^{14}C dose in the urine as did the other high-dose animals (i.e., 71 versus 36%, respectively; $p < 0.01$). In contrast, fecal levels of radioactivity were significantly lower ($p < 0.01$) in the severely affected high-dose rats (19%) than in the remaining seven animals (56%). The urine of iv-dosed rats of both sexes contained approximately 90% of the ^{14}C dose at 5 days after dosing, whereas the feces accounted for 3 to 4%. All tissues combined contained less than 0.5% for all groups, and carcasses accounted for 0.60 to 1.04% (orally dosed rats) and 2.09 to 2.25% (iv-dosed rats). Cage washes of all animals represented about 0.3 to 1.5%.

D. Tissue ^{14}C levels (ppm/wet weight) were low 5 days after dosing; all tissues combined accounted for ≤0.32% of the administered dose, and most tissues contained <1 ppm ^{14}C (Table 2). An exception was the bone, which contained 2.7

TABLE 1. Mean Percent Recovery (± S.D.) of Radioactivity in Rats 5 Days After Oral or Intravenous Administration of [^{14}C]Sulfosate

	Percent of [^{14}C] administered to rats dosed at:							
	25 mg/kg (oral)[a]		250 mg/kg (oral)[a]		25 mg/kg (repeated oral)[b]		25 mg/kg (iv)[a]	
Fraction	Males	Females	Males	Females	Males	Females	Males	Females
Urine	57.0 ± 9.7	50.8 ± 1	56.1 ± 21.7	36.1 ± 12.5	51.6 ± 7.4	47.3 ± 7.6	89.7 ± 2.3	89.6 ± 3.0
Feces	37.4 ± 11.4	38.2 ± 11.6	35.5 ± 22.1	53.5 ± 14.0	42.0 ± 6.6	37.8 ± 4.7	3.34 ± 1.3	3.93 ± 3.21
Tissues[c]	0.20 ± 0.02	0.29 ± 0.07	0.21 ± 0.07	0.31 ± 0.37	0.22 ± 0.05	0.23 ± 0.07	0.32 ± 0.06	0.32 ± 0.09
Carcass[d]	1.04 ± 0.19	1.00 ± 0.16	0.84 ± 0.32	0.60 ± 0.20	0.85 ± 0.15	0.91 ± 0.20	2.09 ± 0.10	2.25 ± 0.32
Cage wash	0.48 ± 0.30	1.41 ± 0.82	1.27 ± 1.06	0.78 ± 0.87	0.29 ± 0.13	1.20 ± 1.02	1.41 ± 1.32	0.39 ± 0.31
Total	96.2 ± 2.5	91.7 ± 8.8	94.0 ± 0.8	91.3 ± 2.7	95.0 ± 3.7	87.5 ± 7.8	96.9 ± 0.06	96.4 ± 1.7

[a]Animals (five or six/sex) were given a single oral or intravenous (iv) dose of [^{14}C]sulfosate.

[b]Animals (five/sex) were given a single oral dose of 25 mg unlabeled sulfosate/kg/day for 14 days followed by a single oral dose of 25 mg [^{14}C]sulfosate/kgon day 15.

[c]Includes total radioactivity in the liver, kidneys, brain, heart, spleen, total skin, small and large intestines, stomach, gonads, gastrointestinal contents, and whole blood.

[d]Includes KOH-soluble and insoluble carcass and separately analyzed femurs.

Source: CBI Tables 1 and 2, CBI pp. 23-25.

TABLE 7. Distribution of Radioactivity in Tissues of Rats 5 Days after Oral or Intravenous Administration of [^{14}C]Sulfosate

	[^{14}C]Sulfosate equivalents (ppm) for rats dosed at:							
	25 mg/kg (oral)[a]		250 mg/kg (oral)[a]		25 mg/kg (repeated oral)[b]		25 mg/kg (iv)	
Organ/Tissue	Males	Females	Males	Females	Males	Females	Males	Females
Liver	0.309 ± 0.077[c]	0.203 ± 0.047	2.260 ± 1.23	1.750 ± 0.640	0.225 ± 0.047	0.190 ± 0.040	0.367 ± 0.060	0.427 ± 0.123
Kidneys	0.311 ± 0.082	0.177 ± 0.042	2.750 ± 1.140	1.560 ± 0.700	0.251 ± 0.063	0.154 ± 0.034	0.530 ± 0.039	0.390 ± 0.048
Brain	0.091 ± 0.0282	0.0607 ± 0.0108	0.766 ± 0.330	0.508 ± 0.163	0.0755 ± 0.0195	0.0611 ± 0.0120	0.168 ± 0.015	0.151 ± 0.027
Small intestine	0.256 ± 0.070	0.457 ± 0.226	1.730 ± 0.806	3.120 ± 4.470	0.429 ± 0.154	0.402 ± 0.176	0.0970 ± 0.0222	0.112 ± 0.038
Large intestine	0.232 ± 0.141	0.246 ± 0.098	2.730 ± 0.930	7.380 ± 5.570	0.251 ± 0.060	0.322 ± 0.157	0.11 ± 0.033	0.117 ± 0.036
Stomach	0.110 ± 0.017	0.189 ± 0.079	1.680 ± 0.620	2.900 ± 0.832	0.136 ± 0.069	0.130 ± 0.0759	0.102 ± 0.022	0.106 ± 0.029
Gonads	0.042 ± 0.0114	0.0924 ± 0.0216	0.407 ± 0.215	0.940 ± 0.653	0.0405 ± 0.0081	ND[d]	0.0671 ± 0.0049	0.123 ± 0.047
Heart	0.0691 ± 0.0124	0.0445 ± 0.0043	0.614 ± 0.244	0.443 ± 0.096	0.0569 ± 0.0133	0.0407 ± 0.0098	0.131 ± 0.018	0.133 ± 0.047
Spleen	0.130 ± 0.0272	0.0908 ± 0.0174	1.060 ± 0.530	0.818 ± 0.201	0.106 ± 0.018	0.0982 ± 0.0208	1.160 ± 0.590	1.510 ± 0.500
Lungs	0.204 ± 0.037	0.145 ± 0.0306	1.370 ± 0.500	1.099 ± 0.351	0.152 ± 0.017	0.124 ± 0.034	0.421 ± 0.051	0.450 ± 0.091
Fat	ND	ND	ND	ND	ND	ND	ND	ND
Muscle	ND	ND	ND	ND	ND	ND	0.287 ± 0.380	ND
Skin	0.0714 ± 0.0220	ND	0.670 ± 0.390	0.779 ± 0.758	ND	ND	0.0760 ± 0.0288	0.0714 ± 0.0241
Bone	3.320 ± 0.530	2.900 ± 0.520*	31.800 ± 14.300	19.400 ± 8.400*	3.220 ± 0.500	2.680 ± 0.440	6.940 ± 0.699	4.610 ± 0.750
Whole blood	0.0373 ± 0.0077	0.0669 ± 0.0088	0.268 ± 0.108	0.173 ± 0.044	0.100 ± 0.042	0.0645 ± 0.0101	0.442 ± 0.148	0.443 ± 0.145

[a]Animals were given a single oral or intravenous (iv) dose of [^{14}C]sulfosate.

[b]Animals were given a single oral dose of 25 mg unlabeled sulfosate/kg/day for 14 days followed by a single oral dose of 25 mg [^{14}C]sulfosate/kg on day 15.

[c]Each value represents the mean (ppm wet weight) and standard deviation of five animals, except for values iv-dosed males, which represent the mean and standard deviation of six animals.

[d]Not detected.

*Significantly different ($p < 0.05$).

Source: CBI Tables 4 and 6, CBI pp. 30-31 and 34-35.

to 7 ppm for low-dose rats and 19.4 to 31.8 ppm for high-dose rats. The ^{14}C levels in liver, kidneys, lungs, and intestines of low- and repeated-dose animals were between 0.2 and 0.5 ppm. Similar to slightly higher ^{14}C concentrations were found in the spleen, liver, kidneys, lungs, and whole blood of iv-dosed animals. Tissue ^{14}C levels in high-dose rats were proportinately higher than those in low- and repeated-dose animals. Bone ^{14}C levels in high-dose females were significantly higher ($p < 0.05$) than those of low-dose female rats. Whole blood of both orally and intravenously dosed rats contained the lowest levels (<0.45 ppm). Analysis of data indicated no significant retention of ^{14}C in the tissues of repeated-dose rats.

E. Only one major area of radioactivity (R_f 0.6) was seen on TLC plates spotted with urine or fecal extracts (extracts contained 64 to 89% of the total fecal radioactivity). This spot accounted for approximately 87 to 95.5% of the radioactivity in the urine and fecal extracts of single-dose rats (low and high), 77 to 84% of that excreted by repeated-dose rats, and 83 to 92% of that excreted by iv-dosed animals (Table 3). Several other faint spots were seen near the main area; however, these smaller spots generally accounted for less than 3% of the ^{14}C in the urine or in fecal extracts. One metabolite (2A), isolated from the feces of repeated-dose females, represented 8.50% of the extracted fecal ^{14}C of this group. The compound was tentatively identified as aminomethylphosphonic acid because its R_f was similar to the R_f of that standard in the same TLC system (CBI p. 21). Small amounts of radioactivity (0.30 to 2.70%) remained at the origin. Chromatographic and spectral analyses indicated that the major "metabolite" excreted by rats was unchanged parent compound. Other TLC spots were not characterized further, primarily because of insufficient material for analysis.

13. STUDY AUTHOR'S CONCLUSIONS QUALITY ASSURANCE MEASURES:

A. The study authors concluded that low, high, and repeated oral doses of [^{14}C]sulfosate were readily absorbed and excreted by male and female rats. Within 5 days after compound administration, animals eliminated approximately 36 to 57 percent of the ^{14}C dose in the urine and 36 to 54 percent in the feces. The recovery of 90% of the ^{14}C in the urine of iv-dosed rats indicated that urinary levels of radioactivity approximated gastrointestinal absorption of [^{14}C]sulfosate, whereas fecal radioactivity represented the unabsorbed parent compound. Some sex- and dose-related

TABLE 5 Distribution of Metabolites in the Urine and Feces of Rats Dosed Orally or Intravenously with [^{14}C]Sulfosate

Radioactive Spot[c]	Percent of ^{14}C excreted by rats dosed at: 25 mg/kg (oral)[a] Males Urine	Males Feces	Females Urine	Females Feces	250 mg/kg (oral)[a] Males Urine	Males Feces	Females Urine	Females Feces	25 mg/kg (repeated dose)[b] Males Urine	Males Feces	Females Urine	Females Feces	25 mg/kg (iv)[a] Males Urine[d]	Females Urine[d]
1 (origin)	0.75[e]	2.00	0.32	0.51	0.47	1.06	0.57	0.82	0.30	1.52	0.30	2.70	0.53	0.48
2	0.58	1.16	0.96	1.61	0.11	2.44	0.68	1.10	1.87	7.35	1.66	2.66	0.92	1.88
2A	--[f]	--	--	--	--	--	--	--	--	--	--	8.50	--	--
3	0.63	94.83[g]	0.74	95.52[g]	0.26	92.83[g]	0.58	95.26[g]	1.15	84.25[g]	0.97	77.10[g]	1.58	2.34
4	1.5[e]	2.01	4.03	2.27	2.09	3.66	2.13	2.82	3.59	6.87	3.87	9.04	2.19	2.98
5	94.65[g]	--	86.67[g]	--	94.64[g]	--	93.84[g]	--	82.76[g]	--	79.98[g]	--	91.73[g]	82.67[g]
6	1.77	--	5.58	--	2.22	--	2.23	--	7.03	--	9.02	--	2.17	6.25
7	0.06	--	1.59	--	0.19	--	0.27	--	2.80	--	3.82	--	0.76	2.74
8	0.02	--	0.12	--	0.02	--	0.09	--	0.52	--	0.45	--	0.13	0.68

[a]Animals were given a single oral or intraveneous (iv) dose of [^{14}C]sulfosate.

[b]Animals received a single oral dose of 25 mg unlabeled sulfosate/kg/day for 14 days followed by a single oral dose of 25 mg [^{14}C]sulfosate/kg on day 15.

[c]Metabolite numbers for urine and feces do not necessarily correspond to the same spot/metabolite.

[d]Fe[illegible] metabolites of iv-dosed rats were not quantitated.

[e]Val[illegible]s represent the mean of four samples.

[f]Not d[illegible]ected.

[g]Unchanged sulfosate.

Source: CBI Tables 7 and 9, CBI pp. 36 and 38.

unabsorbed parent compound. Some sex- and dose-related differences were observed in the excretion of ^{14}C. For example, high-dose male rats eliminated a larger amount ($p < 0.05$) of radioactivity in the urine and a smaller amount ($p < 0.05$) in the feces than high-dose females. Similarly, high-dose female rats excreted more ($p < 0.05$) of the ^{14}C dose in the feces and less in the urine, when compared with low-dose females. In addition, there appeared to be a sex-independent relationship between the percent of the dose in the urine and the degree of toxicity observed: high-dose animals that had the most severe and prolonged toxic reaction to sulfosate eliminated 71% of the administered ^{14}C dose in the urine, whereas those least affected eliminated only 36% ($p < 0.01$). Thus, animals affected most severely absorbed more parent compound. The authors noted, however, that since food consumption decreased markedly in these animals, it was not possible to determine whether increased absorption was a cause or an effect of the toxicity. Repeated dosing had no effect on the route or rate of elimination of ^{14}C when compared with other groups.

Although ≤0.32% of the ^{14}C dose was found in the tissues of all animals, 0.6 to 2.25% remained in the carcasses, mostly in the bones. The concentration of radioactivity in the bones of all dose groups is suggestive of bioaccumulation.

Unchanged parent compound accounted for approximately 80 to 95% of the total urinary radioactivity in all rats, 93 to 96% of that in fecal extracts of single-dose animals, and 77 and 84% of that in fecal extracts of repeated-dose males and females, respectively. These data indicated that sulfosate administered orally to rats remained mostly unmetabolized. A few minor metabolites were identified; each of these generally accounted for less than 3% of the excreted radioactivity. A compound isolated only from the feces of repeated-dose females was tentatively identified as aminomethylphosphonic acid (AMPA). (AMPA is the principal degradation product of sulfosate in soil and is formed via microbial activity.) Representing 8.50% of the ^{14}C in fecal extracts of high-dose female rats, AMPA may have been formed by intestinal microflora in the gut.

B. A quality assurance/GLP compliance statement, signed and dated July 28, 1989, was included in the report.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

This study was conducted adequately according to EPA guidelines (Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation Human and Domestic Animals, 1984, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, pp. 152-156), and the authors' conclu-

sions were supported by the data presented. Sufficient numbers of animals (five or six/sex/dose) were used, and the doses administered (low; high enough to produce signs of toxicity) and dosing regimens employed (single oral low and high, repeated low, and intravenous) were appropriate.

Orally administered [^{14}C]sulfosate was readily absorbed and eliminated by rats. Approximately 70 to 82 and 85 to 94% of the ^{14}C dose were recovered from the urine and feces within 24 and 120 hours postdosing, respectively. Total recoveries (urine, feces, tissues, carcass, and cage washes) were between 87.5% and 96.9%; the value for repeated-dose females (i.e., 87.5%) was somewhat low, but all others were acceptable(≥ 90%). The recovery of 90% of the iv dose in the urine indicated, as the study authors suggested, that the ^{14}C recovery values for the urine of orally dosed rats represented compound absorbed by the gastrointestinal tract; values for feces approximated the amount of unabsorbed sulfosate. Using fecal values, the reviewers calculated that, except for the high-dose females, all other dose groups absorbed about half of an oral dose of sulfosate. Absorption was significantly lower (<40% of an oral dose, $p < 0.05$) in high-dose females.

In general, tissue levels of radioactivity were low (<3 ppm; ≤0.32% of the ^{14}C dose when combined) 5 days after dosing; in contrast, carcasses contained up to 2.25% of the ^{14}C dose. Analysis of carcasses revealed that nearly all of this residual radioactivity was in the bones. As suggested by the study authors, these data suggested that sulfosate may accumulate in bone.

The reviewers agree with the study authors that sulfosate was not extensively metabolized by rats. However, repeated oral dosing may have caused a slight increase in the metabolism of the parent compound. Approximately 83 to 95.5% of the radioactivity excreted by animals given a single oral or intravenous dose of [^{14}C]sulfosate was parent compound; the corresponding values for repeated-dose rats were between 77 and 84% (Table 3 of this DER). An increase in the amount of certain metabolites excreted explained this shift. For example, metabolite 6 accounted for approximately 2 to 5.5% of the urinary radioactivity of single-dose animals but 7 to 9% of that of repeated-dose rats; similarly, urinary metabolite 7 represented 0.06 to 1.6 and 2.8 to 3.8%, respectively. In addition, approximately 7 to 9% of the fecal radioactivity of repeated-dose rats was metabolite 4, whereas this compound accounted for no more than 3.7% of that excreted by single-dose animals. The feces of repeated-dose males also contained a much larger amount of metabolite 2 than the feces of all other animals (i.e., 7.35% versus 0.92 to 2.44%, respectively). Finally, metabolite 2A, a fecal metabolite excreted by only repeated-dose females, accounted for 8.50% of the ^{14}C in the feces.

Although several of the metabolites listed in Table 3 of this DER represented 5 to 9% of the excreted radioactivity, none other than 2A was characterized further. Sketched TLC autoradiograms indicated that urinary metabolites 6 through 8 and fecal metabolite 4 were more polar than the parent compound. However, no additional information (i.e., R_f values of standards versus unknown metabolites; results of additional chromatographic or spectral analyses) was provided for any metabolite other than 2A, which was tentatively identified as the decarboxylated metabolite aminomethylphosphonic acid (AMPA). The authors' suggestion that AMPA was formed by intestinal microflora seemed reasonable in light of the fact that the compound was found only in fecal samples and that AMPA is the principal microbial degradation product of sulfosate in soil.

The fate of the sulfonium ion was not investigated.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix, Protocol and Protocol Deviations, CBI pp. 46-67.